UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/505,399	08/19/2004	Ioannis Alexander Avramis	ON/4-32344A	7262

1095 7590 10/31/2008

NOVARTIS
CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 104/3
EAST HANOVER, NJ 07936-1080

EXAMINER	
FISHER, ABIGAIL L	

ART UNIT	PAPER NUMBER
1616	

MAIL DATE	DELIVERY MODE
10/31/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/505,399	AVRAMIS ET AL.	
	Examiner	Art Unit	
	ABIGAIL FISHER	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 August 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,10 and 14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,10 and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application went abandoned on September 12 2008 for failure to reply to the Office action mailed on February 1 2008. Applicants have petitioned to revive under 37 CFR 1.137(b). This petition filed on August 28 2008 was granted on October 7 2008.

Receipt of Amendments and Remarks filed on August 28 2008 is acknowledged. Claims 2-9 and 11-13 were/stand cancelled. Claims 1, 10 and 14 were amended. Claims 1, 10 and 14 are pending.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on August 28 2008 was considered by the examiner.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Applicant Claims
2. Determining the scope and contents of the prior art.
3. Ascertaining the differences between the prior art and the claims at issue, and resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 10, and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thiesing et al. (Blood, 2000) in view of Estey et al. (Blood, 1999).

Applicant Claims

Applicant claims a combination of an ATP competitive inhibitor of c-abl kinase activity (N-(5-[4-(4-methyl-piperazino-methyl)-benzoylamido]-2-methylphenyl]-4-(3-pyridyl-2-pyrimidine-amine or a pharmaceutically acceptable salt thereof) and two or more other antineoplastic agents selected from Idarubicine, Fludarabine, and Ara-C. The other antineoplastic agents are independently present in free form or as a pharmaceutically acceptable salt.

Applicant claims a pharmaceutical composition comprising a combination of an ATP competitive inhibitor of c-abl kinase activity (N-(5-[4-(4-methyl-piperazino-methyl)-

benzoylamido]-2-methylphenyl]-4-(3-pyridyl-2-pyrimidine-amine) or a pharmaceutically acceptable salt thereof) and two or more other antineoplastic agents selected from Idarubicine, Fludarabine, and Ara-C. The other antineoplastic agents are independently present in free form or as a pharmaceutically acceptable salt. Optionally added is at least one pharmaceutically acceptable carrier.

Applicant claims a commercial package comprising an ATP competitive inhibitor of c-abl kinase activity and two or more other antineoplastic agents. The active agents are independently present in free form or as a pharmaceutically acceptable salt.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Thiesing et al. (Blood, 2000) is directed to the efficacy of STI-571. It is indicated that in chronic myelogenous leukemia (CML) there are an excess of myeloid cells. These cells differentiate and function as normal. During the progression of the disease there results a loss of terminal differentiation and the disease terminate in an acute leukemia known as blast crisis. This blast crisis is usually of the myeloid phenotype (aka acute myeloid leukemia or AML) (first paragraph). N-(5-[4-(4-methyl-piperazino-methyl)-benzoylamido]-2-methylphenyl]-4-(3-pyridyl-2-pyrimidine-amine) (also known as STI-571) was tested with several other antileukemic agents including daunorubicin and ara-c. Table 1 indicates that a combination of STI-571 and daunorubicin or ara-c respectively resulted in a substantial decrease in the IC60s when compared to STI-571 alone. Idarubicin is a known analog of daunorubicin, as evidenced by the Merck Index. STI-571 was dissolved in a sterile-phosphate-buffered saline. Ara-C and daunorubicin

were dissolved in water (page 3195, Reagents). Both saline and water are acceptable pharmaceutical carriers.

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Theising et al. does not disclose a commercial package comprising an ATP competitive inhibitor of c-abl kinase activity and two or more other antineoplastic agents. Theising et al. does not disclose a combination therapy of STI-571 and FAI. For this reason Estey is relied upon.

Estey et al. is directed to a Phase II study of active agents in treating AML. One drug combination that is disclosed is FAI (fludarabine, ara-C and idarubicin) (table 1). The dosages of these drugs were given on sequential days (page 2479, left column 2nd paragraph).

Finding of Prima Facie Obviousness Rational and Motivation (MPEP §2142-2143)

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine STI-571 and FAI into combination chemotherapy. One of ordinary skill in the art would have a reasonable expectation of success as Theising et al. teaches that combinations of STI-571 and ara-c or daunorubicin (an idarubicin analog) respectively, were already known to produce synergistic results. Additionally, it would have been obvious to one of ordinary to include anti-neoplastic agents that are known to treat AML because it was known in the art that CML exhibits the same type of blast crisis that is seen in AML. Therefore one of ordinary skill in the art would have had a

reasonable expectation that a combination of STI-571 and FAI would exhibit at least an additive effect.

As a general principle it is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose, the idea of combining them flows logically from their having been individually taught in the prior art. See *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) **MPEP 2144.06.**

Absent any unexpected results, and based upon the teachings of the prior art, there would have been a reasonable expectation of success in practicing the instantly claimed invention.

Further, it would have been obvious to one of ordinary skill in the art to package the drug in a commercial package. One of ordinary skill in the art would have been motivated to do this because these drugs will be utilized together and therefore it would have been obvious to have provided them in a package that would have resulted in them being kept together. The combined packaging would have provided for easier commercial sale, where a customer only has to purchase one package as opposed to several. This would have resulted in a bigger appeal to the customer because of the ease of purchasing this particular combination therapy.

Other Matters

Applicant has indicated synergistic results. The table in example 1, which is drawn to one particular active combination, indicates that a synergistic effect is seen

only with ED50 and ED70 concentrations. However, the ED90 concentration is merely additive. Example 3, which is drawn to a different active combination, indicates that a synergistic effect is seen with ED50, ED70 and ED90 concentrations. This indicates that at certain concentrations there is an additive effect while at other concentrations there is a synergistic or antagonist effect. Theising et al. indicate that a synergistic effect is seen with STI-571 and ara-c or daunorubicin (an idarubicin analog) respectively, at IC60 concentrations. Therefore applicant would have to compare STI-571 and two or more other antineoplastic agents to the synergistic effect seen with STI-571 and ara-c or idarubicin respectively. This would indicate that there is a synergistic response seen with STI-471 and two or more other antineoplastic agents and not merely additive to the known synergistic response seen with STI-571 and one other antineoplastic agent such as ara-c and daunorubicin (an idarubicin analog). Therefore the currently presented claims are not commensurate in scope with the purported "unexpected results".

Response to Arguments

Applicants argue that (1) the synergistic results shown in the prior art are only for the combination of ara-C and STI571 and that these synergistic effects appear to only be in bcr-abl positive CML cell lines. Therefore, since Estey et al. do not study the FAI combination of drugs in bcr-abl, one of ordinary skill in the art would not have a reasonable expectation of success. Applicants argue that (2) the unexpected results shown in the specification is sufficient to support the patentability of the presently claimed invention. Applicants argue that (3) Theising et al. are silent with respect to

combinations of three or more agents and makes no suggestion that such combinations should be studied in CML or any other condition.

Applicants' arguments filed August 28 2008 have been fully considered but they are not persuasive.

Regarding applicants' first and third argument, Theising et al. shows that combination of STI-571 and daunorubicin or ara-c respectively resulted in a substantial decrease in the IC60s when compared to STI-571 alone. Therefore, synergistic results are shown with STI571 and two different chemotherapeutic agents. Since Theising et al. teach utilizing combinations of STI571 and daunorubicin or ara-c, it would have been obvious to one of ordinary skill in the art to formulate a pharmaceutical formulation comprising STI-571, daunorubicin, and ara-c. As a general principle it is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose, the idea of combining them flows logically from their having been individually taught in the prior art. See *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) **MPEP 2144.06.** Since Idarubicin is a known analog of daunorubicin, one of ordinary skill in the art would have been motivated to replace daunorubicin with idarubicin as both are taught by Merck Index as functional equivalents. Estey et al. teach the utilization of FAI, which comprises fludarabine, idarubicine, and ara-c. Since two of those chemotherapeutic agents would have been obvious based on the teachings of Theising et al. and the Merck Index, it would have been obvious to one of ordinary skill in the art to utilized FAI as it is a know

chemotherapeutic combination utilized. Additionally, it would have been obvious to one of ordinary to include anti-neoplastic agents that are known to treat AML because it was known in the art that CML exhibits the same type of blast crisis that is seen in AML. Therefore one of ordinary skill in the art would have had a reasonable expectation that a combination of STI-571 and FAI would exhibit at least an additive effect. Consequently, applicants arguments that the teachings of Estey et al. do not teach that the FAI combination of drugs is studied in expressed bcr-abl cell lines is not persuasive as FAI is a known chemotherapeutic combination comprising ara-c and idarubicin, a known analog of daunorubicin and Theising et al. teach that ara-c and daunorubicin can be utilized with STI571 in a synergistic combination.

Regarding applicants' second argument, synergistic results between STI571 and the chemotherapeutic agents ara-c and daunorubicin is known. Therefore applicant would have to compare STI-571 and two or more other antineoplastic agents to the synergistic effect seen with STI-571 and ara-c or idarubicin respectively. This would indicate that there is a synergistic response seen with STI-471 and two or more other antineoplastic agents and not merely additive to the known synergistic response seen with STI-571 and one other antineoplastic agent such as ara-c and daunorubicin (an idarubicin analog). Therefore the currently presented claims are not commensurate in scope with the purported "unexpected results".

Therefore, the rejection is maintained since applicant has not provided any persuasive arguments to overcome the rejection.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ABIGAIL FISHER whose telephone number is (571)270-3502. The examiner can normally be reached on M-Th 9am-6pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Abigail Fisher
Examiner
Art Unit 1616

AF

/Mina Haghighatian/
Primary Examiner, Art Unit 1616